REMARKS/ARGUMENTS

Prior to the present amendment, claims 23-28, 40-52 and 64-73 were pending in this application. Claims 23, 24, 27, 43, 44, 46, 47, 67, 68, 70 and 71 have been amended. The amendments are of formal nature and do not add new matter. All amendments were made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing application.

Claim Rejections - 35 U.S.C. § 112

Claims 23-28, 40-52, and 64-73 remained rejected under 35 U.S.C. 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention." In particular, claims 23, 47 and 71 were held "indefinite" in their recitation of "a significant level of phosphorylation." The claims have been amended to recite that the presence of phosphorylation is detected. This amendment is clearly supported by the Examples, which illustrate various methods for detecting the presence of phosphorylation. In view of the teaching provided in the specification including, but not limited to, the Examples, and also in view of general knowledge in the art, one of ordinary skill would clearly understand what detection of the presence of phosphorylation means, and would have no difficulty understanding what applicants regard as their invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. § 102

(a) Claims 23-28, 40, 42, 46-52, 64, 66, and 70 remained rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Thor *et al.* (J. Clin. Oncol. 18(18):3230-3239 (2000)).

(b) Claims 23-28, 40, 42-44, 47-52, 64, and 66-68 remained rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Wildenhain *et al.* (Oncogene, 5(6):879-883 (1990)).

(c) Claims 23-28, and 42-44 remained rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Xu *et al.* (Int. J. Cancer, 59:242-247 (1994)).

(d) Claims 23-28, and 42-44 remained rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Ignatoski *et al.* (Endocrinology, 140:3615-3622 (1999)).

(c) Claims 23-28, 40, 42-44, 47-52, 64, 66 and 70 were newly rejected under 35 U.S.C. 102(b) as allegedly being anticipated by DiGiovanna.

Although, with regard to the maintained rejections (a)-(d), the Examiner has acknowledged that the cited references do not disclose the same intended use as the intended use set forth in the claims, she concluded that the "identifying" or "predicting" steps recited in the claims as amended in response to the previous Office Action "are not considered to be active steps . . . rather are considered to be recitations of mental activity," and thus cannot be relied on to distinguish over prior art. (Page 3 of the Office Action.)

While Applicants strongly disagree with the Examiner's conclusion, for the sole purpose of expediting prosecution, the claims have been amended to recite that the tumor cells or subjects, as applicable, are treated with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, following a determination that such treatment is likely to be successful. Since all rejected claims recite the additional active step of treatment, a step not taught or suggested by the cited prior art, the withdrawal of the maintained rejections (a)-(d) is respectfully requested.

In new rejection (e), the Examiner suggests that DiGiovanna's method "may have the same intended use as the intended uses of the claimed methods with respect to the broad claims of predicting efficacy of a treatment directed to inhibiting signaling by Her2." (Office Action, page 17). It is noted that none of the claims are directed to "predicting efficacy of a treatment directed to inhibiting signaling by Her2" in general. All claims are clearly drawn to methods that predict responsiveness of HER2 positive tumor to treatment with a certain class of HER2 antibodies, namely antibodies that inhibit the association of HER2 with another member of the ErbB receptor family. It is submitted that DiGiovanna does not teach the use of their method to identify responsiveness with the type of antibodies recited in the rejected claims, and does not teach the active step of "treating," which is now recited in all rejected claims. Accordingly, the present rejection should be withdrawn.

Claim Rejections – 35 U.S.C. § 103

(1) Claims 23, 41, 47, 65 and 71-73 remained rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DiGiovanna *et al.* (Cancer Res. 55:1946-1055 (1995)) in view of Terstappen (US 6,365,362, issued April 2, 2002). In response to Applicants' arguments addressing a similar rejection in the previous Office Action, the Examiner cites teaching from DiGiovanna et al. allegedly suggesting that it is highly likely that measuring of p185(Her2) signaling activity as opposed to abundance would enhance methods that use detection of p185 for prognosis and treatment decisions, and that tumors most vulnerable to anti-p185 antibodies will be those that are dependent upon p185 signaling for growth. The Examiner acknowledges that DiGiovanna fails to teach the method using samples of circulating tumor cells.

Terstappen is cited for its alleged teaching that carcinoma cells in the blood may be assayed immunocytochemically to characterize circulating tumor cells.

In addressing Applicants' earlier arguments, the Examiner notes that the small sample size of DiGiovanna is not relevant for the conclusion of obviousness, and that the combination of DiGiovanna with Terstappen makes obvious the claimed methods, even if they recite the use of circulating tumor cells. Just as in the previous rejections, the Examiner disregards the "identifying" and "predicting" steps when interpreting the claims, considering them as mental steps not suitable for distinguishing over prior art.

The rejection is respectfully traversed.

All rejected claims are directed to the identification of tumor cells responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family. In addition, all rejected claims, as currently amended, recite a treatment step. Therefore, even if the "identifying" or "predicting" steps were not active steps, a conclusion with which Applicants strongly disagree, the claims would still be distinguished over the cited combination in their recitation of a treatment step, which is not disclosed or suggested by the cited combination of references.

Applicants maintain that the small sample size on which DiGiovanna's tentative conclusions are based is highly relevant for obviousness considerations for the reasons explained in Applicants' response to the previous Office Action. In order to avoid unnecessary duplications, Applicants' earlier arguments are expressly incorporated herein by reference.

In addition, the claims are directed to methods that concern identification/prediction of responsiveness of HER2-positive (HER2-expressing but not necessarily overexpressing) tumors to treatment with certain types of HER2 antibodies (antibodies inhibiting the association of HER2 with another member of the ErbB receptor family). DiGiovanna *et al.* provide no information, whatsoever, about HER2-positive cancer in general. In addition, DiGiovanna does not provide any information that would establish a link between phosphorylation of the HER2 receptors and responsiveness to treatment with the class of antibodies the use of which is recited in the rejected claims.

The secondary reference, Terstappen was cited for its teaching that carcinoma cells in the blood may be assayed immunocytochemically to characterize circulating tumor cells, and does not remedy the deficiencies of the primary reference.

Accordingly, the combination of DiGiovanna *et al.* and Terstappen does not make obvious the invention claimed in the rejected claims, which now recite a treatment step with certain types of antibodies, and the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 23, 43, 45, 47, 67 and 69 remained rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DiGiovanna *et al., supra.*

According to the rejection, DiGiovanna demonstrates an immunoblot technique, where a phosphor-ErbB receptor band on a gel is detected and separately an immunohistochemistry technique using a phospho-specific anti-ErbB2 receptor antibody. In addition, DiGiovanna is stated to teach that the prior art teaches methods of quantification of tyrosine receptor phosphorylation in tumor samples by immunoprecipitation of receptors and then immunoblottting with an anti-phosphotyrosine antibody, and that such experiments are subject to inaccurate interpretations because of variability in tissue content of stroma/normal cells versus tumor cells and because of tumor cell heterogeneity. From this, the Examiner concludes that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used DiGiovanna's immunohistochemical method to confirm earlier results obtained by immunoprecipitation followed by immunoblotting. Just as in the previous rejections, the Examiner notes that the "identifying," "predicting," and "determining" steps are not considered active steps.

DiGiovanna has been discussed above. In addition, without acquiescing to the Examiner's position, the claims now recite that the tumors/patients identified as likely to be responsive to treatment with antibodies inhibiting the association of HER2 with another member of the ErbB receptor family and treated with an antibody having such characteristics. Thus, the claims unquestionably contain an "active step," which, for reasons discussed above, is not made obvious by DiGiovanna.

Rejection under 35 U.S.C. 112, first paragraph – written description

(1) Claims 23-28, 40-52, and 64-73 have been rejected as allegedly failing to comply with the written description prong of 35 U.S.C. 112, first paragraph due to their recitation of a "significant level of phosphorylation," for which, in the Examiner's view, the specification does not provide adequate written description.

Without acquiescing to the rejection or the Examiner's arguments advanced in support of the rejection, the claims no longer recite a "significant level of phosphorylation," and therefore the present rejection is moot.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge the fees for extension of time, and any additional fees that may be required, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0114A**.

Respectfully submitted,

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